

(FILE 'HOME' ENTERED AT 11:28:36 ON 12 APR 2006)

FILE 'CAPLUS, EMBASE, USPATFULL' ENTERED AT 11:29:03 ON 12 APR 2006

```
L1      120 FILE CAPLUS
L2      101 FILE EMBASE
L3       1 FILE USPATFULL
TOTAL FOR ALL FILES
L4      222 S CYP1A (2A) INHIBIT?
L5       0 FILE CAPLUS
L6       0 FILE EMBASE
L7       0 FILE USPATFULL
TOTAL FOR ALL FILES
L8       0 S L4 AND (TERPINOID?)
L9       0 FILE CAPLUS
L10      0 FILE EMBASE
L11      0 FILE USPATFULL
TOTAL FOR ALL FILES
L12      0 S L4 AND (TERPENOID?)
L13      0 FILE CAPLUS
L14      0 FILE EMBASE
L15      0 FILE USPATFULL
TOTAL FOR ALL FILES
L16      0 S DERMAL CYTOCHROME A450 1A
L17      0 FILE CAPLUS
L18      0 FILE EMBASE
L19      0 FILE USPATFULL
TOTAL FOR ALL FILES
L20      0 S CYTOCHROME A450
L21      0 FILE CAPLUS
L22      0 FILE EMBASE
L23      0 FILE USPATFULL
TOTAL FOR ALL FILES
L24      0 S CYTOCHROME (3A) A450
L25     124099 FILE CAPLUS
L26     81285 FILE EMBASE
L27     13498 FILE USPATFULL
TOTAL FOR ALL FILES
L28     218882 S CYTOCHROME
L29     1348 FILE CAPLUS
L30      969 FILE EMBASE
L31     4396 FILE USPATFULL
TOTAL FOR ALL FILES
L32     6713 S "1A" AND L28
L33      696 FILE CAPLUS
L34      662 FILE EMBASE
L35       28 FILE USPATFULL
TOTAL FOR ALL FILES
L36     1386 S "1A" (3A) L28
L37       1 FILE CAPLUS
L38       0 FILE EMBASE
L39       1 FILE USPATFULL
TOTAL FOR ALL FILES
L40      2 S DERMAL (1S) L36
L41       0 FILE CAPLUS
L42       0 FILE EMBASE
L43       0 FILE USPATFULL
TOTAL FOR ALL FILES
L44      0 S L36 AND (TERPENOID?)
L45      1 FILE CAPLUS
L46      1 FILE EMBASE
L47      0 FILE USPATFULL
TOTAL FOR ALL FILES
L48      2 S L36 AND (TERPEN?)
L49     22806 FILE CAPLUS
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L50 43674 FILE EMBASE  
 L51 4995 FILE USPATFULL  
 TOTAL FOR ALL FILES  
 L52 71475 S ( CYTOCHROME (3A) P450)  
 L53 0 FILE CAPLUS  
 L54 0 FILE EMBASE  
 L55 0 FILE USPATFULL  
 TOTAL FOR ALL FILES  
 L56 0 S ( CYTOCHROME (3A) A450)  
 L57 12 FILE CAPLUS  
 L58 19 FILE EMBASE  
 L59 27 FILE USPATFULL  
 TOTAL FOR ALL FILES  
 L60 58 S ( CYTOCHROME (3A) P450) (1S) TERPEN?  
 L61 6 FILE CAPLUS  
 L62 10 FILE EMBASE  
 L63 15 FILE USPATFULL  
 TOTAL FOR ALL FILES  
 L64 31 S ( CYTOCHROME (3A) P450) (1S) TERPENOID?  
 L65 6 FILE CAPLUS  
 L66 7 FILE EMBASE  
 L67 6 FILE USPATFULL  
 TOTAL FOR ALL FILES  
 L68 19 S ( CYTOCHROME (3A) P450) (20A) TERPENOID?  
 L69 0 FILE CAPLUS  
 L70 0 FILE EMBASE  
 L71 0 FILE USPATFULL  
 TOTAL FOR ALL FILES  
 L72 0 S ( CYTOCHROME (3A) P450) (5A) (INHIBIT?) (20A) TERPENOID?  
 L73 0 FILE CAPLUS  
 L74 2 FILE EMBASE  
 L75 1 FILE USPATFULL  
 TOTAL FOR ALL FILES  
 L76 3 S ( CYTOCHROME (3A) P450) (5A) (INHIBIT?) (2S) TERPENOID?  
 L77 0 FILE CAPLUS  
 L78 0 FILE EMBASE  
 L79 0 FILE USPATFULL  
 TOTAL FOR ALL FILES  
 L80 0 S ( CYTOCHROME (3A) (P450 OR P-450)) (5A) (INHIBIT?) (20A) TER  
 L81 1 FILE CAPLUS  
 L82 0 FILE EMBASE  
 L83 0 FILE USPATFULL  
 TOTAL FOR ALL FILES  
 L84 1 S ( CYTOCHROME (3A) (P450 OR P-450)) (5A) (INHIBIT?) (20A) TE  
 L85 5980 FILE CAPLUS  
 L86 4559 FILE EMBASE  
 L87 842 FILE USPATFULL  
 TOTAL FOR ALL FILES  
 L88 11381 S ( CYTOCHROME (3A) (P450 OR P-450)) (5A) (INHIBIT?)  
 L89 18 FILE CAPLUS  
 L90 10 FILE EMBASE  
 L91 59 FILE USPATFULL  
 TOTAL FOR ALL FILES  
 L92 87 S L88 AND TERPEN?  
 L93 13 FILE CAPLUS  
 L94 7 FILE EMBASE  
 L95 54 FILE USPATFULL  
 TOTAL FOR ALL FILES  
 L96 74 S L88 AND (TERPENIOL OR TERPENE?)  
 L97 18 FILE CAPLUS  
 L98 10 FILE EMBASE  
 L99 59 FILE USPATFULL  
 TOTAL FOR ALL FILES  
 L100 87 S L88 AND (TERPENIOL OR TERPEN?)

L101            20 DUP REM L97-98 (8 DUPLICATES REMOVED)

=> fil uspatful

L101 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1

AB The Ginkgo biloba extract EGb761 was tested for its ability to **inhibit** the major human **cytochrome P 450** enzymes (CYPs). The full extract was found to strongly inhibit CYP2C9 ( $K_i=14\pm4$   $\mu\text{g/mL}$ ), and to a lesser extent, CYP1A2 ( $K_i=106\pm24$   $\mu\text{g/mL}$ ), CYP2E1 ( $K_i=127\pm42$   $\mu\text{g/mL}$ ), and CYP3A4 ( $K_i=155\pm43$   $\mu\text{g/mL}$ ). The **terpenoidic** and flavonoidic fractions of the extract were tested sep. against the same P450s to identify the source of inhibition by EGb761. The **terpenoidic** fraction inhibited only CYP2C9 ( $K_i=15\pm6$   $\mu\text{g/mL}$ ) whereas the flavonoidic fraction of EGb761 showed high inhibition of CYP2C9, CYP1A2, CYP2E1, and CYP3A4 ( $K_i$ 's between 4.9 and 55  $\mu\text{g/mL}$ ). The flavonoidic fraction was further fractionated using extraction and chromatog. Inhibition studies indicated that the majority of these fractions inhibited P450s at a significant level ( $\text{IC}_{50}<40$   $\mu\text{g/mL}$ ).

ST Ginkgo CYP450 enzyme flavonoids **terpenoids** ginkgolides bilobalide EGb761

IT Flavonoids

Natural products, pharmaceutical

**Terpenes**, biological studies

RL: BSU (Biological study, unclassified); NPO (Natural product occurrence); PAC (Pharmacological activity); BIOL (Biological study); OCCU (Occurrence)

(inhibition of human P 450 enzymes by multiple constituents of Ginkgo biloba extract)

AN 2004:409598 CAPLUS

DN 141:33296

L101 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2

TI **Inhibition** of human **cytochromes P450** by components of Ginkgo biloba

AB The extraction, isolation and characterization of 29 natural products contained in Ginkgo biloba have been described, which we have now tested for their in-vitro capacity to **inhibit** the five major human **cytochrome P 450** (CYP) isoforms in human liver microsomes. Weak or negligible inhibitory activity was found for the **terpene** trilactones (ginkgolides A, B, C and J, and bilobalide), and the flavonol glycosides. However 50% inhibitory activity ( $\text{IC}_{50}$ ) was found at concns. less than 10  $\mu\text{g mL}^{-1}$  for the flavonol aglycons (kaempferol, quercetin, apigenin, myricetin, tamarixetin) with CYP1A2 and CYP3A. Quercetin, the biflavone amentoflavone, sesamin, as well as (Z,Z)-4,4'-(1,4-pentadiene-1,5-diyl)diphenol and 3-nonadec-8-enylbenzene-1,2-diol, were also inhibitors of CYP2C9. The  $\text{IC}_{50}$  of amentoflavone for CYP2C9 was 0.019  $\mu\text{g mL}^{-1}$  (0.035  $\mu\text{M}$ ). Thus, the principal components of Ginkgo biloba preps. in clin. use (**terpene** trilactones and flavonol glycosides) do not significantly inhibit these human CYPs in-vitro. However, flavonol aglycons, the biflavonol amentoflavone and several other non-glycosidic constituents are significant in-vitro inhibitors of CYP. The clin. importance of these potential inhibitors will depend on their amts. in ginkgo preps. sold to the public, and the extent to which their bioavailability allows them to reach the CYP enzymes in-situ.

IT Glycosides

RL: PAC (Pharmacological activity); BIOL (Biological study)

(flavonoid; **inhibition** of human **cytochromes**

**P 450** by components of Ginkgo biloba)

IT Ginkgo biloba

Human

(**inhibition** of human **cytochromes P**

**450** by components of Ginkgo biloba)

IT 117-39-5, Quercetin 520-18-3, Kaempferol 520-36-5, Apigenin 529-44-2, Myricetin 603-61-2, Tamarixetin 607-80-7, Sesamin 1617-53-4, Amentoflavone 15291-75-5, Ginkgolide A 15291-76-6,

Ginkgolide C 15291-77-7, Ginkgolide B 33570-04-6, Bilobalide  
103304-56-9 107438-79-9, Ginkgolide J 329322-82-9, Cytochrome CYP3A  
330196-64-0, Cytochrome CYP1A2 774599-66-5

RL: PAC (Pharmacological activity); BIOL (Biological study)

(inhibition of human cytochromes P  
450 by components of Ginkgo biloba)

AN 2004:713139 CAPLUS

DN 141:343409

L76 ANSWER 3 OF 3 USPATFULL on STN

SUMM In avocado tissue, alcohols, aniline, p-chloro-N-methylaniline, N, N-dimethylaniline, cinnamic acid, dimethyl formamide, aryl hydrocarbons and fatty acids showed binding to cytochromes P450. See, S. Cottrell, et al., "Studies on the cytochrome P-450 of avocado (*Persa americana*) mesocarp microsomal fraction" *Xenobiotica* 20: 711-726 (1990). In recent reviews of molecular cloning, plant pathways included cytochromes P450 catalysis of oxygen insertion for fatty acids, phenylpropanoids, flavonoids, **terpenoids**, alkaloids, dyes, pesticides (see, e.g., G. P. Bolwell, et al., "Review Article Number 96. Plant Cytochrome P450" *Phytochemistry* 37: 1491-1506 (1994)); lignins, coumarins, pigments, alkaloids, jasmonates and plant growth regulators (see, M. A. Schuler "Plant Cytochrome P450 Monooxygenases" *Critical Reviews in Plant Sciences* 15(3): 235-284 (1996)). Metolachlor is a herbicide that is detoxified by cytochromes P450 (see, D. E. Moreland, et al., "Metabolism of Metolachlor by a Microsomal Fraction Isolated from Grain Sorghum (*Sorghum bicolor*) Shoots" *Z. Naturforsch* 45c: 558 (1990)). Beneficial effects of flower inducement implicate binding of carbamates to cytochromes P450 (see, M. Kusakawa, et al., "N-(3,4-Methylenedioxyphenyl)carbamates as Potent Flower-Inducing Compounds in *Asparagus* Seedlings as Well as Probes for Binding to Cytochrome P-450" *Z. Naturforsch* 50c: 373 (1995)), where known **inhibitors of cytochromes P450** including piperonyl butoxide and trans-cinnamic acid 4-hydroxylase stopped the effect. The hormonal action of the ecdysone-like brassinosteroids that regulate various aspects of plant development is related to CYP90 genes (see, M. Szekeres, et al., "Brassinosteroids rescue the deficiency of CYP90, a cytochrome P450 controlling cell elongation and de-etiolation in *Arabidopsis*" *Cell* (Cambridge) 85: 171 (1996)). Salicylate and aspirin caused elevation of rat liver ethanol inducible cytochromes P450 (see, B. Damme, et al., "Induction of hepatic cytochrome P4502E1 in rats by acetylsalicylic acid or sodium salicylate" *Toxicology* 106: 99-103 (1996)) and, although salicylates in plants are associated with systemic acquired resistance, their relationships to plant cytochromes P450 has not been demonstrated (see, e.g., S. A. Bowling, et al., "A Mutation in *Arabidopsis* That Leads to Constitutive Expression of Systemic Acquired Resistance" *The Plant Cell* 6: 1845-1857 (1994)). Phenobarbital has been shown to enhance the activity of CYP.sub.cc in non-photosynthetic plant tissue cultures. See, J. Palazon, et al., "Effects of auxin and phenobarbital on morphogenesis and production of digitoxin in *Digitalis* callus" *Plant and Cell Physiology* 36: 247 (1995).

ACCESSION NUMBER: 2000:12751 USPATFULL  
TITLE: Methods and compositions for enhancing cytochrome P450 in plants  
INVENTOR(S): Nonomura, Arthur M., 311 Depot Rd., Boxborough, MA, United States 01719  
Benson, Andrew A., 6044 Folsom Dr., La Jolla, CA, United States 92037  
Nishio, John N., 519 S. 8th St., Laramie, WY, United States 82070-3917

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6020288		20000201
APPLICATION INFO.:	US 1997-927415		19970911 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1996-610928, filed on 5 Mar 1996, now patented, Pat. No. US 5846908 which is a continuation-in-part of Ser. No. US 1995-399399, filed on 6 Mar 1995, now abandoned which is a continuation-in-part of Ser. No. US 1994-351348, filed on 9 Dec 1994, now patented, Pat. No. US 5597400 which is a continuation-in-part of Ser. No. US 1992-901366, filed on 19 Jun 1992, now abandoned		

DOCUMENT TYPE: Utility  
FILE SEGMENT: Granted  
PRIMARY EXAMINER: Clardy, S. Mark  
LEGAL REPRESENTATIVE: Nields, Lemack & Dingman  
NUMBER OF CLAIMS: 38  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 1 Drawing Figure(s); 1 Drawing Page(s)  
LINE COUNT: 2176  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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AN 85042200 EMBASE

DN 1985042200

TI Bifonazole, a biochemist's view.

AU Berg D.; Plempel M.

CS Bayer AG, Pharma Forschungszentrum, D-5600 Wuppertal, Germany

SO Dermatologica, (1984) Vol. 169, No. SUPPL. 1, pp. 3-9. .  
CODEN: DERAAC

CY Switzerland

DT Journal

FS 037 Drug Literature Index  
030 Pharmacology  
013 Dermatology and Venereology  
029 Clinical Biochemistry

LA English

ED Entered STN: 10 Dec 1991  
Last Updated on STN: 10 Dec 1991

AB Bifonazole, a new broad-spectrum antimycotic, interferes with sterol biosynthesis. Compared to clotrimazole, the primary mode of action of these two antimycotics is accepted to represent **inhibition** of the **cytochrome P450**-dependent hydroxylation at the sterol-C14-methyl group, which is the first step in the C14-demethylation reaction. At least in dermatophytes bifonazole additionally inhibits directly HMG-CoA-reductase, the starting and regulatory enzyme in **terpenoid** biosynthesis, whereas after application of clotrimazole the activity of HMG-CoA-reductase is only decreased by feed-back control, resulting from accumulation of dihydrolanosterol. The inhibition of HMG-CoA-reductase obviously is pathogen specific as the mammalian enzyme is not affected. In contrast to clotrimazole, bifonazole possesses a sequential mode of action, namely **inhibition** of **cytochrome P450**-dependent C14-demethylation of sterols and direct inhibition of HMG-CoA-reductase. In vitro bifonazole shows a strongly pH-dependent efficacy. The uptake kinetics of bifonazole have been measured with different pathogens. With respect to budding cells of *Candida albicans* it can be shown that the pH dependence of the efficacy is due to a parallel pH dependence of the intracellular concentration of the active ingredient. Even sublethal concentrations of bifonazole cause prior damage to young cells of *C. albicans*. These effects might explain the loss of infectivity of *C. albicans* after incubation with sublethal concentrations of bifonazole.

CT Medical Descriptors:  
\*biosynthesis  
\*drug indication  
\*pharmacology  
\*drug therapy  
candida albicans  
priority journal  
therapy  
liver  
review  
human  
nonhuman

L76 ANSWER 1 OF 3 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN  
 AN 2004213910 EMBASE  
 TI Inhibition of human P450 enzymes by multiple constituents of the Ginkgo biloba extract.  
 AU Gaudineau C.; Beckerman R.; Welbourn S.; Auclair K.  
 CS K. Auclair, Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Que. H3A 2K6, Canada. karine.auclair@mcgill.ca  
 SO Biochemical and Biophysical Research Communications, (11 Jun 2004) Vol. 318, No. 4, pp. 1072-1078. .  
 Refs: 47  
 ISSN: 0006-291X CODEN: BBRCA  
 PUI S 0006-291X(04)00909-X  
 CY United States  
 DT Journal; Article  
 FS 030 Pharmacology  
 037 Drug Literature Index  
 LA English  
 SL English  
 ED Entered STN: 17 Jun 2004  
 Last Updated on STN: 17 Jun 2004  
 AB The Ginkgo biloba extract EGb761 was tested for its ability to **inhibit** the major human **cytochrome P450** enzymes (CYPs). The full extract was found to strongly inhibit CYP2C9 (K(i)=14±4µg/mL), and to a lesser extent, CYP1A2 (K(i)=106±24µg/mL), CYP2E1 (K(i)=127±42µg/mL), and CYP3A4 (K(i)=155±43µg/mL). The **terpenoidic** and flavonoidic fractions of the extract were tested separately against the same P450s to identify the source of inhibition by EGb761. The terpenoidic fraction inhibited only CYP2C9 (K(i)=15±6µg/mL) whereas the flavonoidic fraction of EGb761 showed high inhibition of CYP2C9, CYP1A2, CYP2E1, and CYP3A4 (K(i)'s between 4.9 and 55µg/mL). The flavonoidic fraction was further fractionated using extraction and chromatography. Inhibition studies indicated that the majority of these fractions inhibited P450s at a significant level (IC (50)<40µg/mL). .COPYRG. 2004 Elsevier Inc. All rights reserved.  
 CT Medical Descriptors:  
 enzyme inhibition  
 fractionation  
 drug isolation  
 chromatography  
 statistical significance  
 microsome  
 medicinal plant  
 Ginkgo biloba  
 human  
 controlled study  
 human cell  
 article  
 priority journal  
 Drug Descriptors:  
 \*Ginkgo biloba extract: PD, pharmacology  
 \*cytochrome P450: EC, endogenous compound  
 cytochrome P450 2C9: EC, endogenous compound  
 cytochrome P450 1A2: EC, en

TI Metabolism of all-trans, 9-cis, and 13-cis isomers of retinal by purified isoenzymes of microsomal **cytochrome P450** and mechanism-based **inhibition** of retinoid oxidation by citral

AB The involvement of a series of microsomal cytochrome P 450 (P 450) isoenzymes in all-trans-retinoid metabolism, including the conversion of all-trans-retinal to all-trans-retinoic acid, was previously described. In the current study, we examined the role of seven liver microsomal P 450 isoenzymes in the oxidation of three isomers of retinal. P 450 1A1, which was not tested previously, is by far the most active in the conversion of all-trans-, 9-cis-, and 13-cis-retinal to the corresponding acids, as well as in the 4-hydroxylation of all-trans- and 13-cis retinal. In contrast, P450s 2B4 and 2C3 are the most active in the 4-hydroxylation of 9-cis-retinal, with turnover nos. .apprx.7 times as great as that of P 450 1A1. The inclusion of cytochrome b5 in the reconstituted enzyme system is without effect or inhibitory in most cases but stimulates the 4-hydroxylation of 9-cis-retinal by P 450 2B4, giving a turnover of 3.7 nmol of product/min/nmol of this isoenzyme, the highest for any of the retinoid conversions we have studied. Evidence was obtained for two addnl. catalytic reactions not previously attributed to P 450 oxygenases: the oxidation of all-trans- and 9-cis-retinal to the corresponding 4-oxo derivs. by isoform 1A2, and the oxidative cleavage of the acetyl ester of vitamin A (retinyl acetate) to all-trans-retinal, also by isoform 1A2. The physiol. significance of the latter reaction, with a Km for the ester of 32  $\mu$ M and a Vmax of 18 pmol/min/nmol of P 450, remains to be established. We also examined the effect on P 450 of citral, a **terpenoid  $\alpha,\beta$ -unsatd. aldehyde** and a known inhibitor of cytosolic retinoid dehydrogenases. Evidence was obtained that citral is an effective mechanism-based inactivator of isoenzyme 2B4, with a KI of 44  $\mu$ M as determined by the oxidation of 1-phenylethanol to acetophenone, and by isoenzyme 1A2 in the oxidation of all-trans-retinal to the corresponding acid and by isoenzyme 2B4 in the 4-hydroxylation of all-trans-retinol and retinoic acid. Thus, citral is not suitable for use in attempts to distinguish between retinoid conversions catalyzed by dehydrogenases in the cytoplasm and by P 450 cytochromes in the endoplasmic reticulum.

IT 9035-51-2, Cytochrome p450, biological studies

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(isoenzymes; metabolism of all-trans, 9-cis, and 13-cis isomers of retinal by purified isoenzymes of microsomal **cytochrome P 450** and mechanism-based **inhibition** of retinoid oxidation by citral)

IT 9035-39-6, Cytochrome b5

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(metabolism of all-trans, 9-cis, and 13-cis isomers of retinal by purified isoenzymes of microsomal **cytochrome P 450** and mechanism-based **inhibition** of retinoid oxidation by citral)

IT 5392-40-5, Citral

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(metabolism of all-trans, 9-cis, and 13-cis isomers of retinal by purified isoenzymes of microsomal **cytochrome P 450** and mechanism-based **inhibition** of retinoid oxidation by citral)

IT 116-31-4, all-trans-Retinal 472-86-6, 13-cis-Retinal 514-85-2, 9-cis-Retinal

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(metabolism of all-trans, 9-cis, and 13-cis isomers of retinal by purified isoenzymes of microsomal **cytochrome P 450** and mechanism-based **inhibition** of retinoid oxidation by citral)

AN 1996:175042 CAPLUS  
DN 124:249621